ELECTRON SPIN RESONANCE SPECTROSCOPY STUDIES OF ^{99}Tc(IV) IN AQUEOUS SOLUTIONS*,†

Walter R. Benson, George C. Yang,‡ Martin W. Heitzmann, and Leonard A. Ford
Food and Drug Administration, Division of Drug Chemistry,
Washington, D.C. 20204
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SUMMARY

The esr spectra of Tc(IV) in acidic, aqueous solutions were observed at ambient temperatures when various reducing agents were added to pertechnetate solutions. The interaction between the $4d^3$ electrons of Tc(IV) and its nucleus ($I = 9/2$) gave 10 hyperfine lines with an average splitting of about 140 gauss. Relative to the rapid reduction rate of TcO_4^-(VII) to Tc(V) using ascorbic acid, the reduction rate of Tc(V) to Tc(IV) as monitored by esr is slow.

Key Words: Aqueous ESR Spectrum, Technetium ^{99}Tc(IV), Radiopharmaceuticals, Ascorbic Acid Reduction

INTRODUCTION

The chemistry of reduced technetium ^{99m}Tc in radioactive drugs is only poorly understood (1). Yet technetium ^{99m}Tc is used more frequently than any other radionuclide in the preparation of commercial radioactive drugs (2). It would be useful to be able to distinguish among the several compounds containing technetium in the oxidation states of III, IV, and V. Of these three oxidation states, the Tc(IV) would be preferable for quantitation and detection, since it is central for oxidation to Tc(V) and reduction to Tc(III). In searching for a

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‡Division of Chemistry and Physics.

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system which would not disturb the environment of Tc(IV) nor be adversely affected by the presence of Tc(V) or Tc(III), we explored the use of electron spin resonance (esr) spectroscopy. ^{99}Tc is available in macroquantities and is easy to handle, even though it also is radioactive, and it has a much longer half-life than ^{99m}Tc.

Schwochau and co-workers (3a, 3b) have reported the hyperfine and superhyperfine esr spectrum of Tc(IV) in a tin dioxide single crystal at 1.7°K. Cotton et al. reported a powder esr spectrum of $[Tc_2Cl_8]^{3-}$ at 77°K and 4.2°K in frozen solution (4). Hambright et al. (5) also mentioned working at low temperatures with several ^{99}Tc compounds but did not give experimental data or details. Bratu et al. (6) observed a broad line for technetium in solution and at room temperature.

We found that esr analysis of K_2TcCl_6 prepared as a solution (7) resulted in a well defined esr spectrum containing 10 hyperfine lines (see Fig. 1) with an average splitting of about 140 gauss. This spectrum was similar to the spectrum reported (3) for a doped SnO_2 crystal at 1.7°K. The product containing technetium was also identified chromatographically as $TcCl_6^{=}$, according to Skukla (8). This procedure excludes the Tc(V) chloride ion, $TcCl_6^-$, because of its R_f value. The TcO_4^- was excluded by use of a diphenylcarbazide spray reagent which produced a color with TcO_4^- but not with $TcCl_6^{=}$. The R_f values for TcO_4^- and $TcCl_6^{=}$ were too close to distinguish by radiochromatogram scanning.

We attempted to prepare the $TcCl_6^{=}$ anion via another route but we obtained at least one different compound. Because radioactive drugs often contain ascorbic acid and/or stannous chloride in physiological saline solution to reduce the ^{99m}Tc, NH_4TcO_4 was reacted with excess ascorbic acid and concentrated HCl. This solution was diluted to 3M HCl and observed by esr. Signal production appeared to arise from a single reaction (see Fig. 2). Formation of Tc(IV) appeared to be rapid at first but was not complete even after 1600 min of reaction time. The final product gave a spectrum identical to that obtained from K_2TcCl_6 (Fig. 1). However, chemically the two substances did not behave the same; the Tc(IV) derived from the HCl-ascorbic acid complex gave an immediate color reaction with concentrated aqueous ammonia, whereas the K_2TcCl_6 derived from KI in concentrated HCl gave no immediate change either in color or by its esr signal. A parallel effect was observed with the paper chromatographic spray reagent diphenylcarbazide: The ascorbic acid complex reacted, but the KI product did not.

Because an insoluble non-chromatographable radioactive ^{99m}Tc material appears at the origin of a paper chromatogram as TcO_2 (99m) in radioactive drugs, the synthesis of TcO_2 (99) was investigated. Gorski and Koch (9) prepared TcO_2 by precipitation from an aqueous solution of hydrazine hydrate and perchloric acid. When we used hydrazine sulfate and dilute H_2SO_4, we were unable to observe a precipitate or see a Tc(IV) esr signal in solution. The directions were vague, however, and we were not able to reproduce the conditions. Nelson, Boyd and Smith (7) reported the synthesis of TcO_2 using Zn and HCl on TcO_4^-. We obtained two NH_4OH-insoluble black solids and a filtrate under these conditions, but no esr signals for Tc(IV) could be detected in the products.

In an attempt to determine the effects of non-aqueous solvents, a solution of $TcCl_6^=$ in aqueous HCl was warmed and evaporated nearly to dryness; the product was divided and added to acetonitrile, dimethyl sulfoxide, and water, respectively. No important changes were detected in the spectra. However, when the HCl solution was taken completely to dryness, the product was not completely soluble in acetonitrile. When this acetonitrile solution was analyzed by esr, the spectrum was altered. Along with the 10 Tc(IV) lines, a strong single line was observed, superimposed on the sixth line from the left (low field) side of Fig. 3.

It is possible that TcO_2 was obtained by one or more of these procedures (7,9). The absence of a Tc(IV) esr signal may be caused by strong coupling between neighboring Tc atoms.

Chloride ion was common to nearly all of these reactions. In an attempt to avoid this ligand, $HClO_4$ (1M), ascorbic acid and NH_4TcO_4 were reacted in aqueous media. The resulting mixture of solution and brown precipitate gave no esr signal.

Howard and Weber (10) reported that TcO_4^- was reduced to Tc(V) by ascorbic acid in 3M HCl within minutes. This product could be complexed with thiocyanate ion to give a deep red color. To test the stability of what we now considered to be a relatively stable complex of Tc(IV), namely, $TcCl_6^=$ ion (in 3M HCl), we added thiocyanate ion in 3M HCl. The esr signal was rapidly lost but there was none of the broadening which might be expected if substitution was occurring. At the same time, a red color formed rapidly. More work is needed to rule out the formation of Tc(III) as a possibility, but oxidation, followed by substitution, appeared to be occurring.

Deutsch et al. (1) reported, on the basis of single crystal X-ray crystallographic studies, that their dimethylglyoxime technetium tin oxychloride complex contained Tc in the V oxidation state. We prepared this complex in approximately 5M HCl, obtaining a red species which finally changed to green, and found no esr signal from Tc(IV). Terry and Zittel (11) indicated that green or yellow was more associated with Tc(III) at buffered pH 7 and 4.7, respectively. Deutsch et al. (1) reported that their crystal was yellow, and it appeared to precipitate after the $SnCl_2$ in solution was completely oxidized to the Sn(IV) state (12). Thus, Tc(IV) may not be present except as a transitory state.

Based on serial dilution of a Tc(IV) solution B (see Experimental section) containing 6.1×10^{-3}M Tc in 3M HCl, esr could be used to detect and quantitate about 5.7×10^{-4}M Tc as Tc(IV), equivalent to about 5.7×10^{-9} mole of ^{99}Tc, since the active region in an esr cell generally contained 15 µl of solution.

When we used stainless steel needles to transfer small quantities of acidic solutions of ^{99}Tc from one closed vial to another, a distinctive 6 line spectrum was detected in all esr spectra. We attribute this to the presence of Mn(II) ion. We now avoid direct contact with steel at pH values below 4. Above pH 4, the pH region of most of the commercial kits used to prepare radiopharmaceuticals, Mn(II) from stainless steel instruments did not present a problem.

Work on commercial kits using ^{99}Tc was complicated by the lack of high concentrations of $SnCl_2$ and/or ascorbic acid and possibly by the lack of reducing power (13), relative to the amount of ^{99}Tc as TcO_4^- which must be added to obtain a signal. This work is continuing.

EXPERIMENTAL

Materials and Instrumentation. All esr spectra were obtained with a Varian E9 electron spin resonance spectrometer using a 50 µl flat quartz cell. All radiochromatograms were scanned with a Varian Berthold instrument equipped with a windowless gas-flow detector. The source of ^{99}Tc was a stock solution containing 55.2 mg of NH_4TcO_4 per ml.

Reduction of Tc(VII) with HCl and KI. A solution of K_2TcCl_6(IV) was prepared according to Nelson et al. (7), using scaled-down proportions as follows: 0.5 ml of NH_4TcO_4 stock solution, 2.00 ml of H_2O, 78 mg of KI and 1.2 ml of 12M HCl were mixed in a vial. Vial and contents were heated in a water bath at 85° for 45 min. A stream of air was used to remove I_2, and HCl was added to replace lost HCl. This solution was designated product A and its esr spectrum was scanned.

Effect of Heat and Solvents on Product A. Three 0.5 ml aliquots of A were evaporated to near dryness with an 85° water bath and a stream of air. The residues obtained were redissolved in acetonitrile, dimethyl sulfoxide and water, respectively, and the esr spectra of the resulting solutions were scanned. All three solutions gave a strong 10 line spectrum of Tc(IV). An aliquot of A was heated on a hot plate to dryness with a stream of air. The residue was heated further until the white-yellow appearance changed to grey. This was thought to indicate possible decomposition. Immediately 1 ml of acetonitrile was added to the still warm vial and a bright, clear green was obtained, but only transiently; in a few seconds it changed to yellowish green. The esr spectrum (Fig. 3) showed the superimposition of a strong single line on the familiar 10 line spectrum.

Reduction of Tc(VII) with HCl and Ascorbic Acid. Into a 10 ml volumetric flask was pipetted 1.00 ml of NH_4TcO_4 stock solution. Then 540 mg of solid ascorbic acid was added, followed by 2.5 ml of 12M HCl. The solution was finally diluted to volume with H_2O and mixed well, and the esr spectrum of an aliquot designated B was obtained. The growth of the esr 10 line spectrum was observed as a function of time (Fig. 2).

Reaction of Tc(IV) Complexes with Base. When concentrated NH_4OH was added in

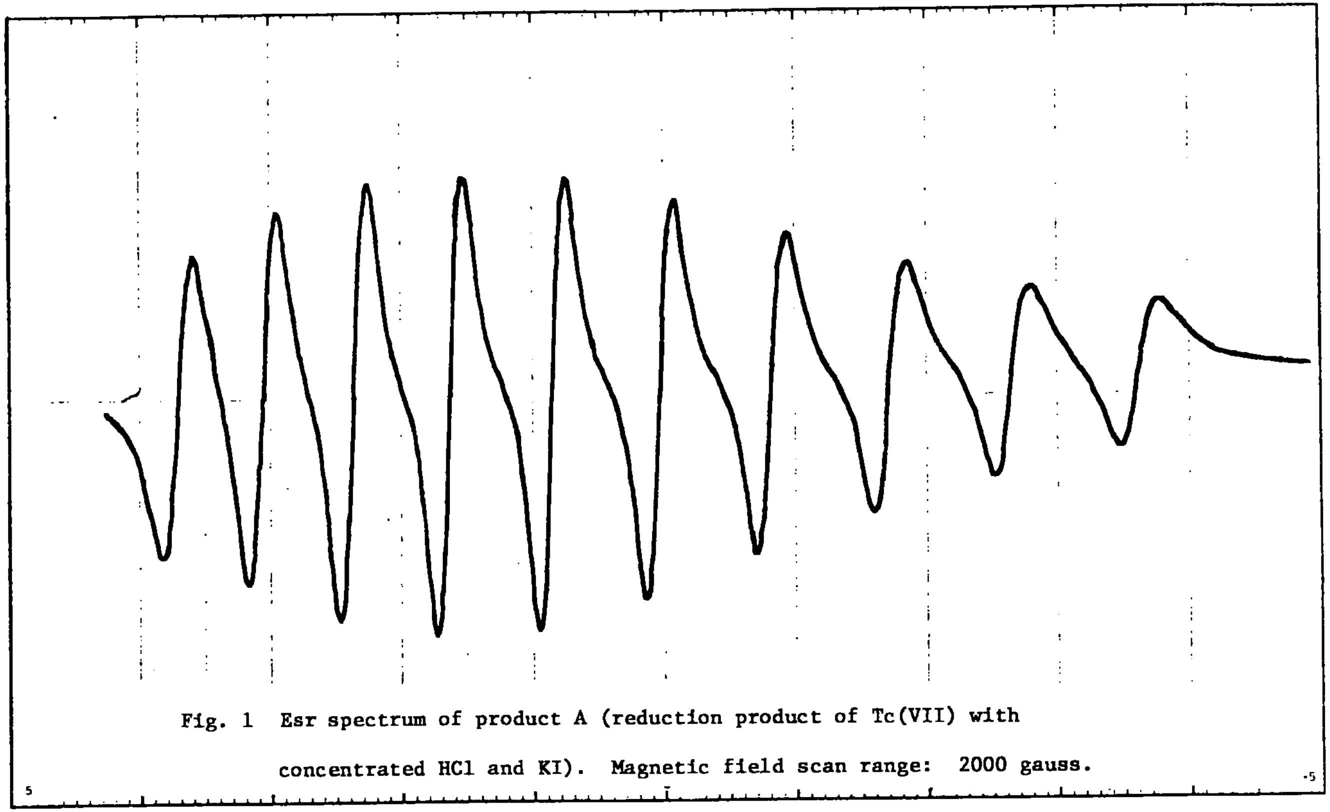

Fig. 1 Esr spectrum of product A (reduction product of Tc(VII) with concentrated HCl and KI). Magnetic field scan range: 2000 gauss.

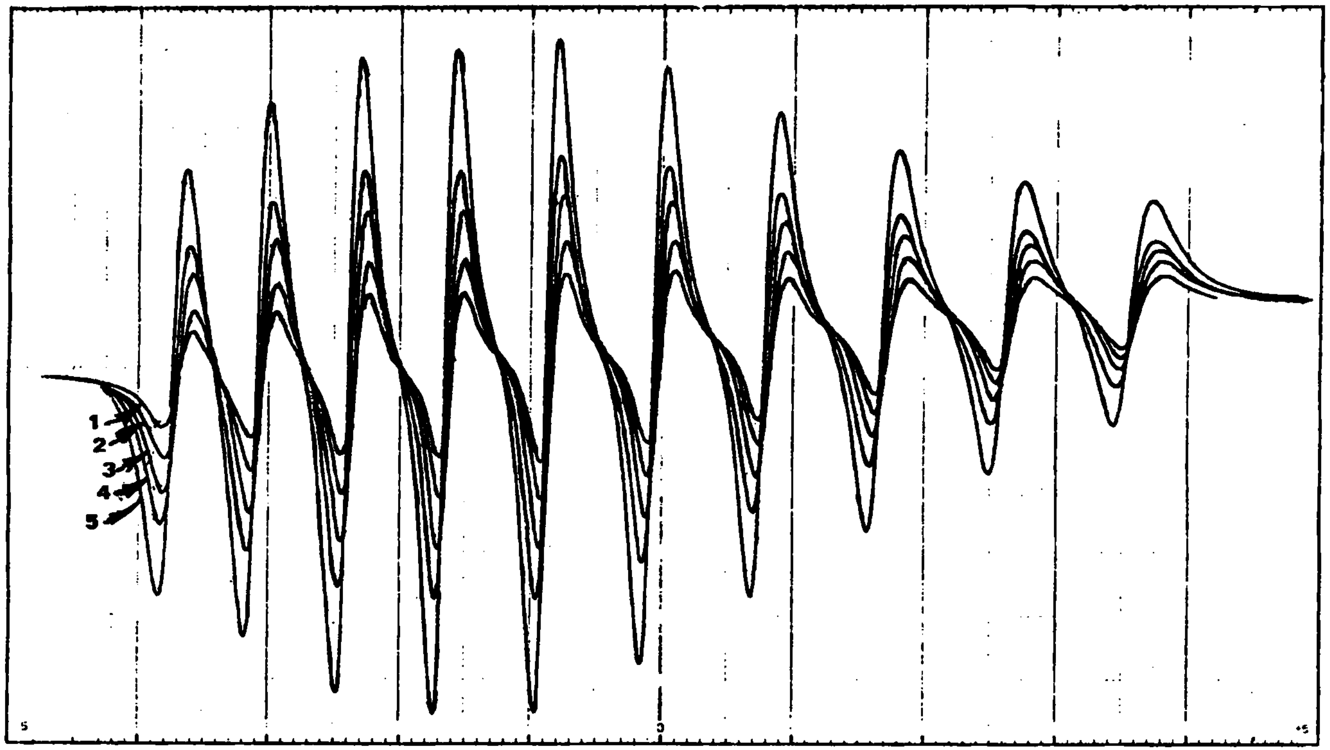

Fig. 2 Time dependent esr spectra of product B (reduction product of Tc(VII) with HCl and ascorbic acid). Magnetic field scan range: 2000 gauss.

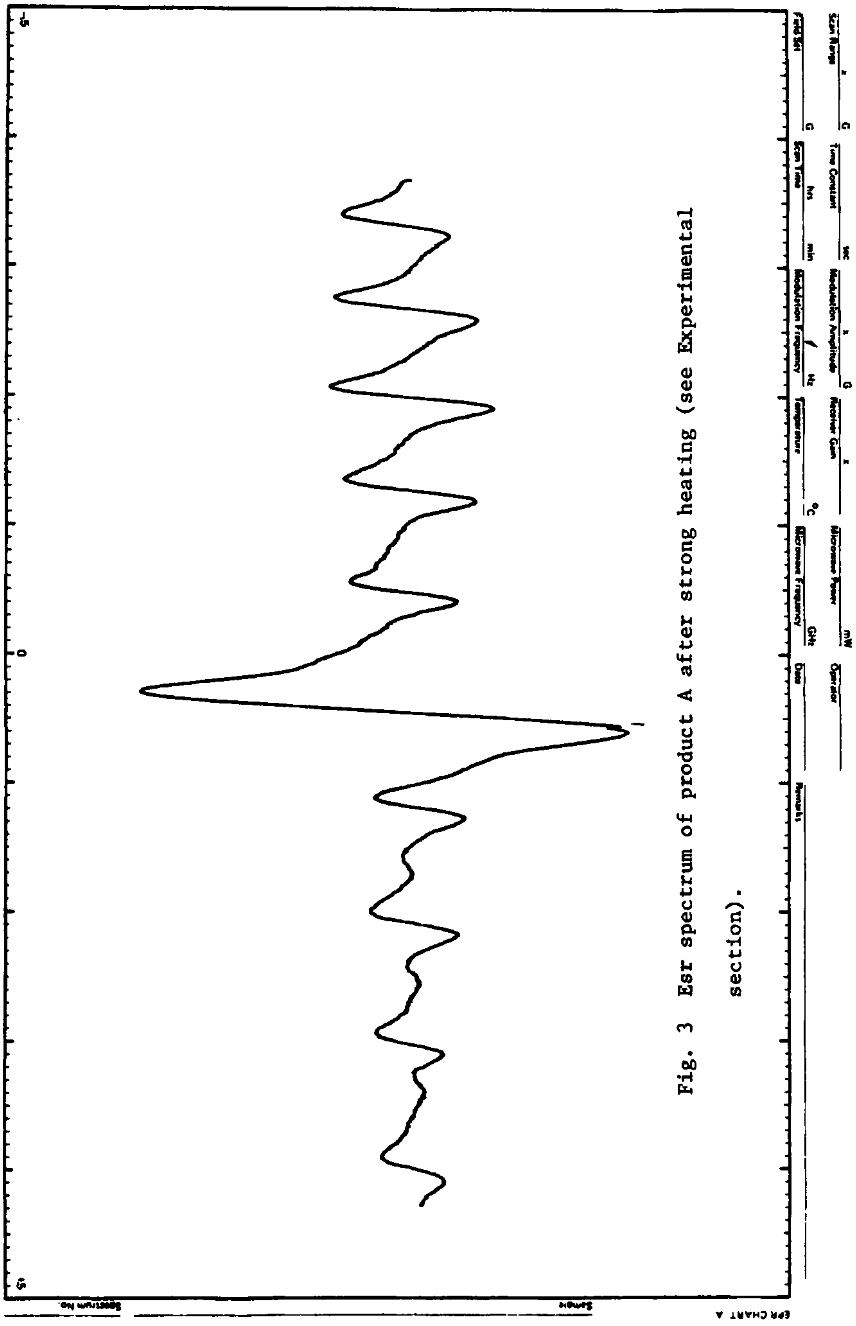

Fig. 3 Esr spectrum of product A after strong heating (see Experimental section).

excess to A and B, respectively, A gave no color change and the esr spectrum decayed slowly or not at all, whereas B gave a deep red color and the esr 10 line spectrum decayed rapidly. At pH 3-5, however, A behaved as before, but B decayed much more slowly.

Paper Chromatographic Behavior of Tc(IV) Complexes. The two products A and B were spotted on Whatman 3 MM paper and chromatographed (ascending) with 0.06M HCl. The R_f values were almost identical by radioscanning, but the diphenylcarbazide spray (14) showed no color with A and a purplish color with B.

Attempted Preparations of TcO_2. The method of Nelson et al. (7) was used to prepare TcO_2. An initial black precipitate (C) was formed after the zinc dissolved in the excess HCl. This solid C was filtered and the filtrate was neutralized with excess NH_4OH. An additional precipitate (D) was formed. Neither C nor D gave an esr signal.

Reaction of Tc(IV) Complexes with Other Reagents. An excess of solid NH_4SCN was added to an aliquot of A. The 10 line esr spectrum decreased to zero amplitude in about 2 hr.

CONCLUSION

Tc(IV) can be detected at room temperature and in solution by esr. Work is needed to find the limits of this detection. It appears that K_2TcCl_6 can be altered so that the 10 line spectrum can collapse to a single line. Based on these observations, the oxidation state of ^{99m}Tc and the structure of radioactive drugs containing ^{99m}Tc should be more closely approached by using compounds containing ^{99}Tc.

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